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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
08/978,633	11/25/1997	ELAZAR RABBANI	ENZ-53	4639

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/978,633	RABBANI ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-255 and 257-303* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-255 and 257-303* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Note that the restriction requirement mailed 12-3-03 is withdrawn. Claims 245-255 and 257-303 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

3. The drawing informalities noted in Paper No. 23, mailed on 12/3/02, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 245-255 and 257-303 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 245 is drawn to a construct which when present in a cell produces a product, said construct having at least one terminus comprising a polynucleotide tail hybridized to a

complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand. Claim 246 specifies wherein the antibody comprises a polyclonal antibody.

Claim 247 is drawn to a composition comprising (a) a non-natural entitity which comprises: at least one domain to a specific nucleic acid component; and at least one domain to a cell of interest; and (b) said specific nucleic acid component; wherein the domain or domains to said nucleic acid component are different from the domain or domains to said cell. Claim 248 specifies that the entity comprises a binder. Claim 249 states that the binder and the domain are the same. Claim 250 specifies that the binder and domain are different. Claim 251 specifies that the binder is a support. Claim 252 specifies that the nucleic acid component is a nucleic acid or nucleic acid component. Claim 253 specifies that the cell is eukaryotic. Claim 254 specifies that the domains are attached noncovalently. Claim 255 specifies that the noncovalent binding is hydrophobic interaction and nonionic interaction. Claim 257 specifies that the specific binding is mediated by a ligand binding receptor. Claim 258 specifies that the ligand binding receptor is a binding ligand to be recognized by its substrate. Claim 259 states that the domain to said nucleic acid component and the domain to said cell of interest are natural, and said binder is attached to said nucleic acid component by means other than a natural binding site. Claim 260 states that the binder comprises modified fibronectin. Claim 261 states that the cell of interest is contained within an organism. Claim 262 states that the composition of claim 247 further comprising said

cell of interest. Claim 303 states the domains are attached noncovalently through specific binding.

Claim 263 is drawn to a method of introducing a nucleic acid component into a cell comprising: (a) providing the composition of claim 247; and (b) administering said composition. Claim 264 states the method of claim 263, wherein administering is carried out in vivo. Claim 265 states the method of claim 263, wherein administering is carried out ex vivo.

Claim 266 is drawn to a kit introducing a nucleic acid component into a cell of interest, comprising in packaged containers or combination; (a) a non-natural entity which comprises at least one domain to said nucleic acid component, and a domain to said cell of interest; (b) a nucleic acid component, optionally with c) buffers and instructions.

Claim 267 is drawn to a composition comprising an entity which comprises at least one domain to a cell of interest, wherein said domain or domains are attached to a nucleic acid component which is in non-double stranded form. Claim 268 states wherein the entity comprises a binder. Claim 269 states that the binder and domain are the same. Claim 270 states wherein the binder and domain are different. Claim 271 states the composition of claim 268, wherein the binder is a support. Claim 272 states that the cell is eukaryotic. Claim 273 states that the nucleic acid component is a nucleic acid or a nucleic acid construct. Claim 274 states the domain is noncovalent binding. Claim 275 states that the noncovalent binding is hydrophobic and non-ionic. Claim 276 states that the domains are attached noncovalently through specific binding. Claim 277 states that the specific binding is mediated by a ligand binding receptor. Claim 278

states that the ligand binding receptor is a binding ligand to be recognized by its substrate. Claim 279 states that the cell of interest is containing within an organism. Claim 280 states that the composition further comprises the cell of interest.

Claim 281 is drawn to a method of introducing a nucleic acid component into a cell comprising: (a) providing the composition of claim 267; and (b) administering said composition. Claim 282 states the administering is carried out in vivo. Claim 283 states that the administering is carried out ex vivo.

Claim 284 is drawn to a kit for introducing a nucleic acid component into a cell of interest, comprising in packaged containers or combinations: (a) an entity which comprises a domain to said cell of interest, wherein said domain is attached to a nucleic acid component which is in non-double stranded form, optionally with (b) buffers and instructions.

Claim 285 is drawn to a composition comprising: an entity which comprises a domain to a nucleic acid component, wherein said domain is attached to a cell of interest. Claim 286 state the entity comprises a binder. Claim 287 states that the binder and the domain are the same. Claim 288 states that the binder and the domain are different. Claim 289 states that the binder is a support. Claim 290 states that the nucleic acid component is a nucleic acid or a nucleic acid construct. Claim 291 states that the cell is eukaryotic. Claim 292 states that the domain is noncovalent binding. Claim 293 states that the noncovalent binding is hydrophobic and non-ionic interactions. Claim 294 states that the noncovalent binding comprises a specific complex. Claim 295 states that the specific complex is mediated by a ligand binding receptor. Claim 296

states that the ligand binding receptor is a binding ligand to be recognized by its substrate. Claim 297 states that the composition of claim 285 comprises the cell of interest. Claim 298 states that the cell of interest is contained within an organism.

Claim 299 is drawn to a method of introducing a nucleic acid component into a cell comprising: (a) providing the composition of claim 285; and (b) administering said composition. Claim 300 is drawn to the method of claim 299 wherein administering is carried out in vivo. Claim 301 is drawn to the method of claim 299, wherein administering is carried out ex vivo.

Claim 302 is drawn to a kit for introducing a nucleic acid component into a cell of interest, comprising in packaged containers or combination: (a) an entity which comprises a domain to said nucleic acid component, wherein said domain is attached to said cell of interest, optionally with (b) buffers and instructions.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

By way of specific design and example, vectors for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data in the specification as filed. Specifically, construction of the M13 phage vectors pRT-A, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense A, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. A modified version of the pINT-3 construct (the parent vector of pRT-A, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-A tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make

pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC

(when the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function

and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The instantly claimed compositions and the methods of delivery of those compositions are considered to lack written description in the specification as filed for a representative number of species of any such composition because the text of the specification as filed provides only general guidance, and not specific guidance, for the design and use of the claimed compounds. The U1-antisense compounds (summarized above) are not considered representative of the genus of instantly claimed constructs which when present in a cell produce a product where said construct has at least one terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence, the construct being bound non-ionically to an entity comprising a chemical modification or a ligand. The U1-antisense cassette vectors do not have noncovalent polymeric interactions. Even though they are composed entirely of polynucleotides in the form of a vector, the polynucleotide units in the U1-cassette vectors are covalently bound to each other.

From the figures and the prophetic examples in the specification as filed, one of skill in the art would not be able to readily envisage a representative number of specific examples of the claimed complexes. Pages 26-28 describe figures 14-21 as follows: figure 14, a divalent antibody binder with one portion having an affinity for binding a retroviral particle, and the other portion having an affinity for binding the CD34 antigen; figure 15, the covalent attachment of

DNA to each portion of an F(ab')2 antibody fragment with an affinity for the CD34 antigen; figure 16(a), the covalent attachment of DNA to an adenovirus binding portion of a divalent antibody in order to promote the binding of an AAV vector DNA molecule to a CD34 receptor, figure 16(B), same as figure 16(a) except that F(ab') fragments are used instead of complete antibody proteins; figure 17, a monovalent antibody to an adenovirus spike protein with one portion being modified by covalent attachment of DNA that can bind an adenovirus associated virus (AAV) vector DNA molecule through hybridization and the other portion being modified by the covalent attachment of an oligolysine modified by the attachment of lactyl groups; figure 18, a monovalent antibody to an adenovirus spike protein in which each portion of the antibody has been modified by the covalent attachment of lactosylated DNA molecules which are bound to an AAV vector DNA by means of hybridization; figure 19, the synthetic steps for producing a reagent that is useful for attaching nucleic acid moieties to an antibody; claim 21, a process for multimerization of F(ab') antibody fragments by hybridization of nucleic acid homopolymers. On pages 39 and 40, the specification generally discusses making CHENAC constructs with ligands and having chemical modifications such as a polynucleotide tail. The paragraph spanning pages 40 and 41, further describes the myriad of interactions possible between the CHENAC constructs and the ligands, such as noncovalent attachment (as instantly claimed). Page 41 of the specification states generally what the ligands may be comprised of, and page 42 states that the cell targeting entities can be antibodies to cellular surface components and epitopes. On page 43, the ligand is described as a matrix protein such as fibronectin that binds to

hematopoietic cells and other cells. Pages 44-45 teach prophetically how the ligands can be introduced into the CHENACs. Page 50 defines the instantly claimed invention as "[i]f the Binder has at least one Domain to a Nucleic Acid Component, then the Binder is attached to a target cell. If the Binder has at least one Domain to both the Nucleic Acid component and the target cell the Domain to the cell is different from the Domain to the Nucleic Acid Component. Page 51 further states that "[a] Binder is a support or matrix that is composed of at least one Domain. A binder can be natural or synthetic, such as a polymer, support, matrix or carrier...," Pages 51-55, and 59-80 further discuss the binder and domain interactions and their use with nucleic acid constructs. On pages 114-119, the specification further discusses use of antibodies and proteins as dislocation agents for aiding the introduction of a construct that produces a product as transport from one cellular locale to another. The description therein is very broad and does not provide a clear picture of specific species that can be readily envisaged by one of skill in the art to have a particular structure which correlates to a specific function.

Examples 1-10 on pages 120-136 of the specification discuss attaching chemical modifications, such as tri-lactyl lysyl lysine to nucleic acid compositions; addition of a fusogenic peptide (page 124) to a DNA primer, etc., but none of these constructs are administered to a cell to produce a product. Examples 11-15 on pages 136-141 of the specification describe prophetically making antibody constructs and binders composed of a bispecific antibody that attaches to a nucleic acid construct component. Example 16 on pages 141-144 describes making Oligo(dA) and oligo (dT) with an amine group at the 5' end synthesized chemically; preparation

of a 1,2 Diamino-4-Bromo-5-Hydroxycyclohexane prepared according to U.S. Patent No. 4,707,440; attachment of a linker to homopolymer; Fab'-SH fragments prepared; and attachment of homopolymer to antibody fragments; and annealing of homopolymers to obtain antibody multimers. However, this example does not describe administration of the complex to cells either in cell culture or in a whole organism, nor production of a product in the cell from the nucleic acid composition as instantly claimed. The only other constructs prophetically described, or described by way of example, were those summarized above, which do not have antibody components, and thus do not adequately describe a representative number of species of the instantly claimed invention.

As pointed out in the previous Office actions, and in the summary of the MPEP provided above, the specification as filed does not adequately describe a representative number of species of the claimed invention unless one of skill in the art would be able to envisage the structure, in this case the chemical structure (nucleic acid, protein, and other claimed chemical compositions, including the cells), of the claimed invention. Since none of the examples, either prophetic or exemplified by reduction to practice, in the specification as filed provide a clear description of the genus and species within the genus of the claimed invention, one of skill in the art would not have recognized that application was in possession of a representative number of species of the claimed invention at the time the invention was made.

Response to Arguments

6. Applicant's arguments filed 06/12/02 have been fully considered but they are not persuasive.

On pages 11-13 of the response filed 06/12/02, application states that "an adequate description has been provided. a detailed description of the constructs of the present invention are provided throughout the specification. For example, the last paragraph on page 47 in their specification states:

> Another significant embodiment of the present invention is a construct which when present in a cell produces a product, the construct being bound non-ionically to an entity comprising either a chemical modification or a ligand addition, or both. As in the case of the other above-described construct, this construct may also comprise at least one terminus, such terminus comprising a polynucleotide tail. The polynucleotide tail is hybridizable or hybridized to a complementary polynucleotide sequence. An antibody to a double stranded nucleic acid can be directed and thus bound to such hybridized polynucleotide tail sequences. The antibody can comprise a polyclonal antibody or a monoclonal antibody.

a detailed description of the compositions of the present invention are provided on pages 48-59. The terms "nucleic acid component", "domain", and "binder" are clearly defined on pages 48-49. Various examples of useful domains are also described. These include useful domains with non-specific cell binding properties (see page 53), useful domains with specific cell binding properties (see page 53), useful domains with specific nucleic acid component binding properties (see page 54). Examples of various binders are provided on page 55. Specific examples of the

constructs and compositions of the present invention are shown in Examples 12-15. Accompanying figures are provided specifically in Figures 16-20."

However, as pointed out above, these "specific examples" are really not specific, but only provide general guidance as to what broad types of compositions are instantly claimed. The descriptions in both the specification and in the figures do not provide an adequate description of specific species, nor representative number of such species, of compositions which may be envisioned to produce a product in a cell, and have an antibody component, as claimed.

Applicant further states that "[s]ufficient identifying characteristics of the constructs, compositions and kits of the present invention is provided as noted above in the specification. Additionally, a sufficient number of species have been disclosed. Finally, Applicants note that actual reduction to practice is not required to satisfy the Written Description Requirement."

In response, although reduction to practice is not required, the MPEP as summarized above, does require for chemical compositions, that one of skill in the art be able to readily envision the claimed constructs, and that the specification provides a clear description of the structure and not just claim the structure by way of functional language. In the instant case, the claims are to constructs which have a certain function, but there is not a representative number of species of any such construct having the claimed functions in the specification as filed. The MPEP states that the identifying characteristics of the composition must be clear. In the instant case, the chemical structure is necessary to envisage the claimed compositions, and the specification has not described the chemical structure of the claimed nucleic acid compositions

nor the antibodies nor other components of the compositions which have the claimed functions in a cell. The stick figures in the drawings do not adequately describe the chemical compositions claimed to the extent that one of skill in the art would be able to readily envisage the administration of the claimed constructs to a cell for producing a product.

7. Claims 263-265, 281-283 and 299-301 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing a nucleic acid product in a whole organism (*in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 245 is drawn to a construct which when present in a cell produces a product, said construct having at least one terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand. Claim 246 specifies wherein the antibody comprises a polyclonal antibody.

Claim 263 is drawn to a method of introducing a nucleic acid component into a cell comprising: (a) providing the composition of claim 247; and (b) administering said composition.

Claim 264 states the method of claim 263, wherein administering is carried out *in vivo*. Claim 265 states the method of claim 263, wherein administering is carried out *ex vivo*.

Claim 281 is drawn to a method of introducing a nucleic acid component into a cell comprising: (a) providing the composition of claim 267; and (b) administering said composition. Claim 282 states the administering is carried out *in vivo*. Claim 283 states that the administering is carried out *ex vivo*.

Claim 299 is drawn to a method of introducing a nucleic acid component into a cell comprising: (a) providing the composition of claim 285; and (b) administering said composition. Claim 300 is drawn to the method of claim 299 wherein administering is carried out *in vivo*. Claim 301 is drawn to the method of claim 299, wherein administering is carried out *ex vivo*.

The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. a second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

By way of specific design and example, vectors for antisense inhibition of HIV in cells by co-expression of antisense DNA under control of a T7 promoter with a T7 polymerase (represented in figures 24-49) are taught and supported by *in vitro* data in the specification as filed. Specifically, construction of the M13 phage vectors pRT-a, pRT-B, and pRT-c are taught which contain the coding sequence for the T7 RNA polymerase driven by the RSV promoter and with an SV40 intron sequence that will be spliced out to form a functional polymerase enzyme and each respective construct also having the antisense a, B, and C sequences driven by a T7 promoter and terminated by a T7 terminator. a modified version of the pINT-3 construct (the parent vector of pRT-a, B and C vectors before insertion of the antisense sequences) is taught where a polylinker is inserted behind the poly-a tail of the T7 polymerase gene for subsequent sub-cloning of the lacZ gene in this instance to form pINT-LacZ. The result upon introduction in a eukaryotic cell would be synthesis of the T7 polymerase from the RSV promoter which in turn acts upon the T7 promoter to synthesize B-galactosidase.

Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasmid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-a, B, C and D were made using the antisense a, B, and C sequences previously described and D as a control containing a non-HIV sequence. a multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make

pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "a" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of pINT-3 (containing the intron containing polymerase) and the T7 promoter driven a, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of a, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense a upstream of B-gal gene where antisense activity of the a portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV a/Anti-a activity and HIV a/Anti-ABC (when

the triple U1 construct was used by *co-transfection*) as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Pages 26-28 describe figures 14-21 as follows: figure 14, a divalent antibody binder with one portion having an affinity for binding a retroviral particle, and the other portion having an affinity for binding the CD34 antigen; figure 15, the covalent attachment of DNA to each portion of an F(ab')2 antibody fragment with an affinity for the CD34 antigen; figure 16(a), the covalent attachment of DNA to an adenovirus binding portion of a divalent antibody in order to promote the binding of an AAV vector DNA molecule to a CD34 receptor, figure 16(B), same as figure 16(a) except that F(ab') fragments are used instead of complete antibody proteins; figure 17, a monovalent antibody to an adenovirus spike protein with one portion being modified by covalent attachment of DNA that can bind an adenovirus associated virus (AAV) vector DNA molecule through hybridization and the other portion being modified by the covalent attachment of an oligolysine modified by the attachment of lactyl groups; figure 18, a monovalent antibody to an adenovirus spike protein in which each portion of the antibody has been modified by the covalent

attachment of lactosylated DNA molecules which are bound to an AAV vector DNA by means of hybridization; figure 19, the synthetic steps for producing a reagent that is useful for attaching nucleic acid moieties to an antibody; claim 21, a process for multimerization of F(ab') antibody fragments by hybridization of nucleic acid homopolymers. On pages 39 and 40, the specification generally discusses making CHENAC constructs with ligands and having chemical modifications such as a polynucleotide tail. The paragraph spanning pages 40 and 41, further describes the myriad of interactions possible between the CHENAC constructs and the ligands, such as noncovalent attachment (as instantly claimed). Page 41 of the specification states generally what the ligands may be comprised of, and page 42 states that the cell targeting entities can be antibodies to cellular surface components and epitopes. On page 43, the ligand is described as a matrix protein such as fibronectin that binds to hematopoietic cells and other cells. Pages 44-45 teach prophetically how the ligands can be introduced into the CHENACs. Page 50 defines the instantly claimed invention as "[i]f the Binder has at least one Domain to a Nucleic Acid Component, then the Binder is attached to a target cell. If the Binder has at least one Domain to both the Nucleic Acid component and the target cell the Domain to the cell is different from the Domain to the Nucleic Acid Component. Page 51 further states that "[a] Binder is a support or matrix that is composed of at least one Domain. a binder can be natural or synthetic, such as a polymer, support, matrix or carrier...," Pages 51-55, and 59-80 further discuss the binder and domain interactions and their use with nucleic acid constructs. On pages 114-119, the specification further discusses use of antibodies and proteins as dislocation agents for aiding the

introduction of a construct that produces a product as transport from one cellular locale to another.

Examples 1-10 on pages 120-136 of the specification discuss attaching chemical modifications, such as tri-lactyl lysyl lysine to nucleic acid compositions; addition of a fusogenic peptide (page 124) to a DNA primer, etc., but none of these constructs are administered to a cell to produce a product. Examples 11-15 on pages 136-141 of the specification describe prophetically making antibody constructs and binders composed of a bispecific antibody that attaches to a a nucleic acid construct component. Example 16 on pages 141-144 describes making Oligo(dA) and oligo (dT) with an amine group at the 5' end synthesized chemically; preparation of a 1,2 Diamino-4-Bromo-5-Hydroxycyclohexane prepared according to U.S. Patent No. 4,707,440; attachment of a linker to homopolymer; Fab'-SH fragments prepared; and attachment of homopolymer to antibody fragments; and annealing of homopolymers to obtain antibody multimers. However, this example does not describe administration of the complex to cells either in cell culture or in a whole organism, nor production of a product in the cell from the nucleic acid composition as instantly claimed. The only other constructs prophetically described, or described by way of example, were those summarized above, which do not have antibody components, and thus do not adequately describe a representative number of species of the instantly claimed invention.

Although the instant claims 263-265, 281-283 and 299-301 do not specifically state that the nucleic acids in the claimed compositions are antisense nucleic acids, the specification as

filed predominantly discusses use of the U1-anti-HIV constructs for administration to cells for antisense downregulation of HIV in the cells. Thus, the claims as written, which involve administration of these nucleic acid compounds to cells, including cells in a whole organism, have a high level of unpredictability in the art analogous to that in the antisense field. Furthermore, for the purposes of the instant rejection, in vivo below is considered to embrace both *in vivo* and *ex vivo* administration as claimed since *ex vivo* administration is also administration of the antisense and cells to a whole organism.

There is a high level of unpredictability known in the antisense art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." When expressed from a vector, the antisense must retain the ability to be localized to the target area. Thus use of U1 introns in the examples in the specification as filed are helpful for targeting the antisense expressed to the nucleus of the cell, but the unpredictability remains for factors such as expression levels of the antisense, the localization of the vector to desired

tissues, and expression of the antisense for the recited function, inhibition of the target gene. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of

subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed compositions, such as one comprising antisense molecules, *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach

(1) stability of the antisense molecule constructs *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

8. Applicant's arguments filed 06/12/02 have been fully considered but they are not persuasive.

Note that the previous rejection of the composition claims are not included in the instant rejection since the reduction to practice of one embodiment is considered representative for enablement purposes of the claimed compositions.

In regards to the Branch and Flanagan references previously cited and reiterated above pertaining to the unpredictability in the art of administration of antisense compounds to cells in a whole organism, applicant argues that they "were actually published after the priority date of the above-referenced application. The MPEP 2164.05(a) states that "the state of the prior art existing at the filing date of the application is used to determine whether a particular disclosure is

enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date reference to demonstrate that the patent is no-enabling.""

In response, the Branch, Flanagan and other newly cited references above are relied upon to teach that even today, there is a high level of unpredictability in the art for design and use of antisense in whole organisms due to the complexity of the whole organism environment and the number of unpredictable factors argued above.

Applicants further "assert that there are a number of publications available as of the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1. Another example is Liu et al., 1997, J. Virol. 71:4079-4085, attached hereto as Exhibit 2 which discloses Tat-activated expression of chloramphenicol acetyltransferase was shown to be specifically inhibited in cells expressing Tat and transactivation response region antisense sequences."

In response, the Liu et al. article is a publication of the constructs and experiments taught in the instant specification. However, the Liu et al. paper does not further provide any *in vivo* context of use for the disclosed constructs. While they state on page 4085 that "[t]he choice of U1 as an antisense carrier provided structural stability and nuclear localization", they further state that "[t]his successful approach in cell culture is being developed as means of achieving a high level of stable resistance in patent cells for the purpose of developing an ex vivo therapy for

treating HIV infections." Thus, the *in vivo* uses are "being developed" and were not show at the time the invention was made to function *in vivo*. The Crook reference does not further provide an specific expectation of success for the instantly disclosed constructs to function *in vivo* either.

Applicant further states that "It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application." Applicants note, however, that clinical trials were underway by the assignee of the instant application around its priority date of the above-referenced application. a press release dated July 1, 1996 is attached hereto as Exhibit 3. The results to date have been favorable and several public announcements regarding the Assignee's clinical trials have been made."

The above rejection does not imply that an animal model of a disease is needed to enable the instantly claimed invention. The rejection is centered on the ability to a make and use the claimed methods with any expression construct as claimed, and the position has been maintained, based on the references cited, that there is a high level of unpredictability in the art of design and use of antisense in a whole organism. Although applicants state that clinical trials are underway, the information in Exhibit 3 does not teach what constructs are in trials and whether or not they function as instantly claimed in the context of a whole organism.

Lastly, "Applicants note that specificity to any degree and certainly 100% specificity is not required of any drug under the patent laws and is evaluated on a case-by-case basis by the

Food and Drug Administration. For example, penicillin is known to be far from specific to a certain target protein of harmful bacteria. However, this does not diminish the importance of penicillin as a useful drug." In response, the issues surrounding penicillin are not analogous to nucleic acid therapeutic compounds such as antisense-type compounds which have a different set of criteria for making and using in a whole organism. While the specification does not need to show that 100% of the claimed invention embodiments are enabled for use at the time the invention was made, the specification does need to overcome the unpredictability in the art with specific direction or guidance as to how to make and use the claimed invention. As put forth above, for the breath of the claimed invention, there is a high level of unpredictability in the art, from which one of skill in the art would necessarily practice an undue amount of experimentation to make and use.

Claim Rejections - 35 USC § 102

9. Claims 247-248, 250-255, 257-259, 262-263, 266-268, 270-281, 284-286, 288-299 and 303 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al. (U.S. Patent 5,574,142).

Claim 247 is drawn to a composition comprising (a) a non-natural entitity which comprises: at least one domain to a specific nucleic acid component; and at least one domain to a

cell of interest; and (b) said specific nucleic acid component; wherein the domain or domains to said nucleic acid component are different from the domain or domains to said cell.

Meyer et al. taught in figure 2 that an antisense oligonucleotide (ODN) which is specific to a nucleic acid of interest inside a cell, is attached via a cleavable peptide linker to a polymer carrier that is a domain that is recognized by an ASGP receptor on the surface of a liver cell.

Claim 248 specifies that the entity comprises a binder. Claim 250 specifies that the binder and domain are different. Claim 251 specifies that the binder is a support. Claim 252 specifies that the nucleic acid component is a nucleic acid or nucleic acid component.

The construct taught by Meyer et al. in figure 2 has a cleavable peptide linker which is a type of binder as instantly claimed. Furthermore, the linker is attached to the polymer carrier which is a domain that is different from the linker/binder. Furthermore, the binder acts as a support to bridge the polymer carrier to the antigene ODN, which is a nucleic acid component.

Claim 253 specifies that the cell is eukaryotic. Claim 262 states that the composition of claim 247 further comprising said cell of interest.

The liver cell taught in figure 2 of Meyer et al. is further described in col. 20 and 21 of Meyer et al. as the Hep G2 cell line, which is a eukaryotic cell line.

Claim 266 is drawn to a kit, which is a composition, comprising (a) a non-natural entity which comprises at least one domain to said nucleic acid component, and a domain to said cell of interest; (b) a nucleic acid component, optionally with c) buffers and instructions. Since Meyer

et al. taught all the limitations of the composition of parts (a) and (b), the construct in figure 2 of Meyer et al., the elements of the claimed kit were taught by Meyer et al.

Claim 254 specifies that the domains are attached noncovalently. Claim 255 specifies that the noncovalent binding is hydrophobic interaction and nonionic interaction. Claim 257 specifies that the specific binding is mediated by a ligand binding receptor. Claim 258 specifies that the ligand binding receptor is a binding ligand to be recognized by its substrate. Claim 259 states that the domain to said nucleic acid component and the domain to said cell of interest are natural, and said binder is attached to said nucleic acid component by means other than a natural binding site. Claim 303 states the domains are attached noncovalently through specific binding.

Figure 2 of Meyer shows that the polymer carrier recognizes and interacts as a ligand to the ASGP receptor, thus the interaction is noncovalent, nonionic and hydrophobic and is not covalently attached. Also, which the polymer carrier ligand is a natural interaction with the ASGP receptor, the cleavable peptide linker is chemically attached to both the antisense ODN and the polymer carrier, which is not a natural interaction.

10. Claims 245, 246, 249, 260, 261, 264, 265, 269, 282, 283, 287, 300 and 301 are considered free of the prior art since the closest prior art to claims 245 and 246, Meyer et al., did not teach that the ODN construct having at least one terminus comprising a polynucleotide tail was hybridized to a complementary polynucleotide sequence and an antibody bound to said hybridized polynucleotide sequence, said construct being bound non-ionically to an entity

comprising a chemical modification or a ligand nor where the binder and the domain are the same (claims 249, 269 and 287); the prior art did not further teach *in vivo* and *ex vivo* use of the construct of Meyer et al. (claims 261, 264, 265, 282, 283, 300 and 301).

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader,* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

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M. M. Schmidt
April 7, 2003